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Note

A convenient synthesis of (*dl*)-3-benzyl-3,4-dihydroisocoumarin as a model of Feralolide

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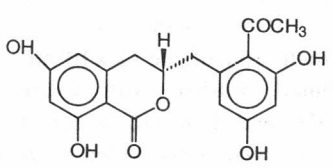
(*dl*)-3-Benzyl-3,4-dihydroisocoumarin **6**, a model of Feralolide, has been synthesized through 3-benzylisocoumarin **2** which is prepared by the condensation of phenylacetyl chloride with homophthalic acid. Alkaline hydrolysis of **2** yielded the keto-acid **3** which is reduced to racemic hydroxy-acid **5**. The latter is cyclodehydrated to furnish the title compound **6**. Isocoumarin **2** and 3,4-dihydroisocoumarin **6** have been screened *in vitro* for their antibacterial activity.

Aloe (or bitter aloe) is a natural drug well known for its cathartic properties[1] and is used as a bittering agent in alcoholic beverages[2]. Speranza *et al.*[3] have reported the isolation, structure elucidation and absolute stereochemistry of a new dihydroisocoumarin named Feralolide **1** from the commercial Cape aloe. In continuation of our syntheses of naturally occurring isocoumarins[4,5] and 3,4-dihydroisocoumarins,[6-8] we report in this article a convenient synthesis of (*dl*)-3-benzyl-3,4-dihydroisocoumarin **6** as a model of Feralolide. 3-Benzylisocoumarin **2** was prepared by the method of Nakajima *et al.*[9] involving direct condensation of phenylacetyl chloride with homophthalic acid (cf. **Scheme I**). The isocoumarin **2** showed characteristic 1H singlet at δ 6.15 for C4-H proton and the lactonic carbonyl absorption at 1718 cm^{-1} in the IR spectrum. Alkaline hydrolysis of **2** afforded the keto-acid **3** which showed a two-proton singlet at δ 3.82 and a one-proton exchangeable broad singlet at δ 10.2 in ^1H NMR spectrum and carbonyl absorptions at 1700 and 1683



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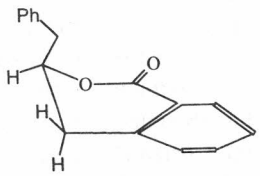

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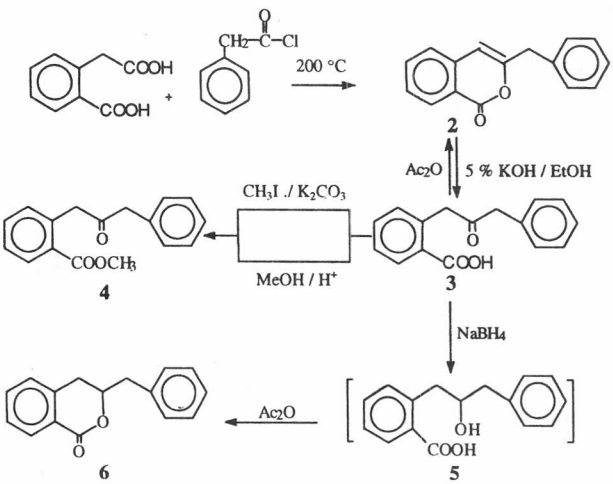

Scheme I

cm^{-1} in IR spectrum. Isocoumarin **2** was obtained back by refluxing the keto-acid **3** with acetic anhydride. Methylation with excess of methyl iodide or with acidic dry methanol with different work-ups yielded the methyl keto-ester **4** which showed carbonyl absorptions at 1720 and 1685 cm^{-1} in IR and a 3H singlet at δ 3.79 in ^1H NMR.

Sodium borohydride reduction of the keto-acid **3** afforded the corresponding hydroxy-acid **5** which was not isolated, but treated directly with acetic anhydride to yield (*dl*)-3-benzyl-3,4-dihydroisocoumarin **6.** It showed carbonyl absorption at 1720 cm^{-1} in its IR spectrum and the typical *ABX* pattern for C4-H and C1'-H protons and *AB* pattern for C3-H proton in ^1H NMR spectrum. The protons of methylene groups adjacent to either side of the chiral center exhibited a diastereotopic effect in ^1H NMR spectrum of 3,4-dihydroisocoumarin **6**. Thus, each of the C4-H protons showed a doublet of doublet (δ 2.98-3.03 and 3.22-3.26). Similarly each of the C1'-H protons appeared as a doublet of doublet (δ 2.81-2.85 and 2.90-2.96). The relatively low coupling constants between C3-H and C4-H_A (7.5 Hz) and between C3-H and C4-H_B (6.0 Hz) provided a strong evidence for the presence of an equatorial hydrogen atom at C-3. Hence, the structure **A** is the proposed structure of **6**. The structures of the synthesised compounds were further confirmed by HREIMS of their molecular ions which were in good agreement with the calculated values.

Antibacterial activity. Screening of 3-benzylisocoumarin **2** and (*dl*)-3-benzyl-3,4-dihydroisocoumarin **6** against different pathogens such as *Bacillus cereus*, *Corynebacterium diphtheriae, Escherichia coli ETEC,*

Kiebsiella pneeumoniae, Proteus mirabilis, Pseudomonas aeroginosa, Salmonella typhi, Shigella boydli, Staphylococcus aureus and *Streptococcus pyogenes* by Agar diffusion protocol (1987) showed low antibacterial activity .

Experimental Section

General. Melting points were determined on a Gallenkamp digital melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi model 270-50 infrared spectrophotometer as KBr discs or as neat liquids. ^{1}H NMR (500 MHz) spectra were recorded on a Bruker AM-500 in $CDCl_3$ solution, using TMS as internal standard. EIMS were recorded on a MAT-112-S machine at 70eV.

3-Benzylisocoumarin 2: Method A. A mixture of homophthallic acid (2.0 g, 11.1 mmoles) and phenylacetyl chloride (6.21g, 45.53 mmoles) was heated at 200 °C with stirring for 3 hr. The residue was purified by column chromatography on silica gel using pet. ether (bp 60-80 °C) as eluent to afford 3-benzyliso-coumarin **2** (1.85g, 7.84 mmoles, 70.6%) as semisolid; IR (KBr): 1718, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.83 (2H, s, H-1'), 6.15 (1H, s, H-4), 7.21-7.45 (5H, m, Ar-H'),7.61-7.64 (1H, ddd, *J* = 1.0, 7.5, 9.0 Hz, H-5), 7.98-8.08 (1H, dt, *J* = 1.0, 2.01, 6.5 Hz, H-7), 8.21-8.23 (1H, dt, *J* = 1.0, 1.5, 8.0 Hz, H-6), 8.36-8.38 (1H, dt, *J* = 1.0, 1.5, 8.0 Hz, H-8); MS: m/z 236 [M$^+$] (100 %), 208 (60.6), 117 (0.8), 105 (19.8).Calcd for $C_{16}H_{12}O_2$: M$^+$, 236.0837. Found: M$^+$, 236.0840.

2-(2'-Oxo-3'-phenylpropyl)benzoic acid 3. A suspension of 3-benzylisocoumarin **2** (0.673 g, 2.85 mmoles) in ethanol (20 mL) and potassium hydroxide (5%, 25 mL) was refluxed for 5 hr. After cooling, the reaction mixture was evaporated to remove ethanol under reduced pressure. Cold water (10 mL) was then added, the reaction mixture acidified with dil. hydrochloric acid, and extracted with dichloromethane (2 × 20 mL), dried (Na_2SO_4) and the solvent rotatory evaporated to give an oil which solidified on standing. The solid was recrystallized from ethyl acetate and pet. ether (bp 60-80 °C) to afford the compound 2-(2'-oxo-3'-phenylpropyl)benzoic acid **3** (0.42 g, 1.65 mmoles, 58 %), mp 132-134 °C; IR (KBr): 1700, 1683, 1598 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.82(2H, H-3') 4.13 (2H, s, H-1'), 7.08-7.36 (5H, m, Ar-H'), 7.38-8.12 (4H, m, Ar-H), 10.2 (1H, s, COOH, D_2O exchangeable); MS: m/z 254 [M$^+$](5.4 %), 236 [M$^+$ – H_2O](88.5), 118 (45.2), 105 (100). Calcd for $C_{16}H_{14}O_3$: M$^+$, 254.0943. Found: M$^+$, 254.048.

3-Benzylisocoumarin 2 from 3 : Method B. Compound **3** (0.1g, 0.39 mmoles) was refluxed with acetic anhydride (0.5 mL) for 12 hr. After cooling, the reaction mixture was poured into ice water and extracted with ethyl acetate (2 × 10 mL). The extracts were combined and washed with sodium bicarbonate (2 × 10 mL, 5%), dried (Na_2SO_4) and concentrated to give an oily product which solidified on standing. The solid was then recrystallized from methanol to afford 3-benzylisocoumarin **2** (0.063g, 0.26 mmoles, 67.3 %) as a semisolid; R_f value, mass, high resolution mass, IR and ^{1}H NMR spectral data were in good agreement with the already synthesized **2** by method A (*vide supra*).

Methyl 2-(2'-oxo-3'-phenylpropyl)benzoate (4): Method A. A mixture of compound **3** (0.15 g, 5.9 mmoles), methyl iodide (in excess) and anhydrous potassium carbonate (1.0 g) in dry acetone (5 mL) was heated under reflux for 3 hr. The reaction mixture was filtered when hot. The resultant cake was washed with warm dry acetone (2 mL) and the solvent evaporated *in vacuo* to afford methyl 2-(2'-oxo-3'-phenylpropyl)-benzoate **4** (0.06 g, 2.2 mmoles, 58.8 %) as an oil; IR (KBr): 1720, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.83 (2H, s, H-3'), 3.79 (3H, s, OMe), 3.87 (2H, s, H-1'), 7.18-7.92 (6H, m, H 3, 4, 5, 3', 4', 5'), 7.96-8.22 (3H, m, H-6, 2', 6'); MS: m/z 268 [M$^+$] (3.15 %), 237 (9.12), 236 (40.14), 149 (11.59), 118 (2.70), 105 (100). Calcd for $C_{17}H_{16}O_3$: M$^+$, 268.1099. Found: M$^+$, 268.1012.

Method B. A solution of compound **3** (0.1 g, 3.9 mmoles) in dry methanol (20 mL) and conc. sulfuric acid (one drop) was refluxed for 3 hr. Water (10 mL) was then added and methanol removed under reduced pressure. Extraction with diethyl ether (2 × 10 mL), followed by removal of solvent and purification by thick layer chromatography furnished methyl 2-(2'-oxo-3'-phenylpropyl)benzoate **4** (0.056g, 0.21 mmoles, 53.6%) as an oil; R_f value, mass, high resolution mass, IR and ^{1}H NMR spectral data were found in agreement with those of **4** already synthesized above by method A.

***(dl)*-3-Benzyl-3,4-dihydroisocoumarin 6.** Compound **3** (0.15 g, 5.9 mmoles) was heated under reflux with sodium borohydride (0.15 g) in absolute ethanol (20 mL) for 6 hr. Ethanol was rotary evaporated, cold water (25 mL) added and the reaction mixture acidified with dil. sulfuric acid to give a precipitate which was extracted with ethyl acetate (2 × 30 mL). The extracts were combined, and the solvent was dried (Na_2SO_4) and evaporated to leave the crude compound **5** (0.12g). This crude compound was dissolved in acetic anhydride (0.7 mL) and heated under reflux for 2 hr. The reaction mixture was cooled, water (10 mL) added to it, then stirred and extracted with dichloromethane (2 ×10 mL). The extracts were combined, washed with sodium bicarbonate (2 × 10 mL, 5%) and then with water (10 mL), dried (Na_2SO_4) and rotary evaporated to leave (*dl*)-3-benzyl-3,4-dihydroisocoumarin **6** as a viscous oil

(0.093 g, 3.9 mmoles, 66.2%); IR (KBr): 1720, 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.81-2.85 (1H, dd, H-1′, J = 3.5 and 16.5 Hz), 2.90-2.96 (1H, dd, J = 11 and 16.5 Hz, H-1'), 2.98-3.03 (*AB*, 1H, dd, J_{vic} = 7.5 Hz, J_{gem} = 14.5 Hz, H-4A), 3.22-3.26 (*AB*, 1H, dd, J_{vic} = 6.0 Hz, J_{gem} = 14.0 Hz, H-4B), 4.70-4.76 (1H, m, H-3), 7.27-7.34 (5H, m, Ar-H'), 7.36-7.39 (1H, ddd, J = 2.5, 7.0, 9.0 Hz, H5), 7.47-7.50 (2H, m, H-6, 7), 8.05-8.07 (1H, dd, J = 1.5, 8.0 Hz, H-8); MS: m/z 238 [M^+] (12 %), 194 (0.4), 118 (100), 106 (0.6), 78 (1.1). Calcd for $C_{16}H_{14}O_2$: M^+, 238.0994. Found: M^+, 238.0997.

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